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In adults with acute diarrhea, which treatment is more effective between loperamide and racecadotril?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

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ABSTRACT

Objective: The objective of this selective EBM review is to determine which treatment is more effective between loperamide and racecadotril to treat acute diarrhea in adults.

Study design: Review of three English language primary randomized controlled studies published from 1999-2005.

Data Sources: First study was a RCT that was double blinded, double placebo, parallel study group and second and third study was RCT single blinded, comparative parallel group that all compared efficacy of loperamide and racecadotril. These were all found by using PubMed, COCHRANE and NCBI.

Outcomes Measured: Each of the studies measured the efficacy of each medication by counting the number of diarrhea stools until recovery was made. Recovery is defined as having 2 consecutive normal stools or having no stools for more than 12 hrs. The number of days the patient had diarrhea were also counted.

Results: Overall, these studies were clinically significant where both racecadotril and loperamide treat acute diarrhea rapidly. It was also observed that loperamide causes more adverse events such as abdominal distention and constipation when compared to racecadotril.

Conclusions: Racecadotril has been shown to be equally effective as loperamide to treat acute diarrhea in these three studies. Racecadotril also effectively resolves abdominal symptoms and causes less constipation than loperamide.

Key Words: Loperamide, Racecadotril, Acute Diarrhea

INTRODUCTION

Diarrhea occurs when either food or liquids are ingested and pass rapidly and/or in large quantities through the colon therefore making it hard for the colon to absorb those excess liquids effectively.[4] This will lead to excess fluid in the colon which then leads to the watery bowel movement known as diarrhea.[4] This paper will evaluate three RCT's in an effort to compare the efficacy of loperamide and racecadotril against acute diarrhea

Infections of the GI tract can lead to acute diarrhea and remains one of the most common causes of acute diarrhea worldwide affecting all ages, races, and genders.[3] Acute diarrhea remains the third most common symptom seen in doctor's offices.[3] Although the mortality rate is not high in this country, there are over 200,000 patients that get hospitalized each year for having acute diarrhea.[5] Inpatient care costs about $2,549 and outpatient care costs about $391 each per patient.[5] Therefore, treating diarrhea in a hospital setting has a large impact on our healthcare system spending.

A variety of different things cause acute diarrhea including viruses, bacteria, certain medications, and certain digestive disorders such as irritable bowel syndrome and inflammatory bowel syndrome.[4] At the onset of the diarrhea, it is important to determine if it will self-resolve or if it needs further medical attention. In about 90% of patients that develop acute diarrhea will resolve on its own.[7] These patients usually respond within five days to rehydration and antidiarrheal medications and would not need a whole diagnostic evaluation.[7] Once acute diarrhea is present for more than seven days or worsening symptoms develop such as fever, abdominal pain, or bloody stools, diagnostic studies are usually done.[7] These studies include stool cultures, complete blood counts, and a complete metabolic panel.[7] These studies will help

determine if the patient will need antibiotic therapy, IV fluids and/or stronger antidiarrheal therapy.[7]

Loperamide is an effective anti-diarrheal medication which has anti-secretory effects and increases intestinal transit time.[1] Because of the increase transit time, it is known for its side effects of rebound constipation and abdominal distention.[1] Racecadotril is being tested as an anti-diarrheal medication because of its anti-secretory properties but at the same time not affecting the intestinal transit time.[1] Comparing the two in studies can show which one is more effective against acute diarrhea in patients.

OBJECTIVE

The objective of this selective EBM review is to determine which treatment is more effective between loperamide and racecadotril for the treatment of acute diarrhea.

METHODS

This review consists of three randomized controlled trials that met specific criteria. The first trial was a RCT that was double blinded, double placebo, parallel group study. The second and third trials were RCT single blinded, comparative parallel group studies. The populations used in these trials were adults greater than 18 years old that have been experiencing diarrhea for at least 24 hrs but for no more than five days. Racecadotril 100 mg was used as the intervention group and loperamide 2mg was used as the comparison group. The outcomes measured were counting the number of episodes of diarrhea and the number of days the patient had diarrhea.

Key words used to research for this topic includes loperamide, racecadotril, and acute diarrhea. All three articles were published in English and published in peer reviewed journals. All articles were researched by the author using PubMed, COCHRANE and NCBI databases. These articles were selected based on relevance to my keywords and topic which could then

answer my POEM question adequately. Inclusion criteria during my search were RCT's that were single or double blinded studies published after 1996. Exclusion criteria during my search were studies that contained patients that were pregnant, under 18 years old and/or had chronic or infectious diarrhea more than five days. Statistics reported and used were control event rate (CER), experimental event rate (EER), relative benefit increase (RBI), absolute benefit increase (ABI), number needed to treat (NNT), confidence interval (CI), p-value, relative risk increase (RRI), absolute risk increase (ABI), and number needed to harm (NNH).

The demographics and characteristics of the studies used in this review are displayed in Table 1.

Table 1: Demographics of included studies

Study	Type	#Pt	Age (yrs)	Inclusion criteria	Exclusion criteria	w/d	Interventions
Prado[1] (2002)	RCT= single-blinded, comparative, parallel group	945	On racecadotril= 35.9 $\pm$ 12.1 On loperamide= 36.4 $\pm$ 13.5	Pt $\geq$ 18yo, having acute diarrhea for at least 24hrs but no more than 5 days. Pt passed 3 watery stools w/in the past 24 hrs.	Pt with chronic, dysenteric bloody, or iatrogenic diarrhea. Pt with acute UC or Pseudomembranous colitis from abx	0	One group given racecadotril 100 mg given 3xdaily. Another group given loperamide 2mg given 3xdaily. Both groups for no more than 7 days.
Vetel[2] (1999)	RCT= double-blinded, double placebo, parallel group study	157	On racecadotril= 40.9 $\pm$ 1.8 On loperamide= 41.5 $\pm$ 2.2	Pt $\geq$ 18yo, having acute diarrhea for at least 24hrs but no more than 5 days	Pt with bloody, purulent, or chronic diarrhea. Pt w/ functional intestinal disorder. Pt started new meds 7days prior or received abx tx 15 days prior to diarrhea. Pt with renal/hepatic insufficiency,HIV positive,DM, or progressive concomitant infection.	8	1st dose: one group given racecadotril 1 capsule (100 mg) and 2 placebo capsules and other group given loperamide 2 capsules (1mg each) and 1 placebo capsule. Thereafter: one racecadotril or loperamide alternating with placebo. Both groups treated for no more than 7 days
Wang[3] (2005)	RCT= single-blinded parallel group study	62	On racecadotril= 38.4 $\pm$ 15.1 On loperamide= 34.7 $\pm$ 12.3	Pt $\geq$ 18yo, having acute diarrhea for at least 24hrs but no more than 5 days. Pt passed 3 watery stools w/in the past 24 hrs.	Pt with bloody,iatrogenic, or chronic diarrhea. Pt w/ fxn intestinal disorder. Pt received abx tx prior to diarrhea. Pt with renal/hepatic dysfunction, immunocompromised,or progressive concomitant infection. Pt tx anti-diarrheal 5 days prior to study.	4	1st group given racecadotril 100mg 3x daily. 2nd group given loperamide 2mg 2x daily. Both groups treated for no more than 7days

					Pregnant or lactating		

OUTCOMES MEASURED

The basis of all outcomes measured in these studies was targeted towards patient oriented evidence that would matter to the patient. The primary efficacy criterion in each study was to count the number of episodes of diarrhea the patient had until recovery or for a maximum of seven days of treatment. Recovery was defined as having two consecutive normal stools or having no stools for more than twelve hours. The number of days the patient experienced diarrhea was also logged into a diary that was given to the patients. Secondary criterion to evaluating safety of medications involved monitoring and recording adverse events such as abdominal distension/pain, constipation, and nausea/vomiting.

RESULTS

In the three following RCT studies, the efficacy of loperamide was compared to the efficacy of racecadotril in the treatment of acute diarrhea. In the Prado study, there were a total of 945 people with acute diarrhea that participated from 21 different primary care clinics in 14 different countries.[1] The duration of diarrhea was monitored starting from the first dose of either loperamide or racecadotril to when the patient had their first formed stool.[1] The duration of diarrhea in both group population was similar with the median duration being 55 hours.[1] The overall clinical response in both groups had high success rates and the calculations for efficacy and safety can be seen in Table 2. In 92% of patients that took racecadotril and 93% of patients that took loperamide had resolution of diarrhea.[1] The NNT was calculated to be -100 and is interpreted as followed: out of 100 patients treated with racecadotril, one less patient would experience complete resolution of diarrhea. This shows that racecadotril is not more or less effective than loperamide. Adverse events were also monitored and were seen in 19% of the total patients.[1] Out of this percentage, it was determined that 14.2% of patients on racecadotril and

23.9% of patients on loperamide had adverse events during the study.[1] These adverse events include patients experiencing constipation, abdominal distention/pain, anorexia, and headaches. With the exception of headache, the other adverse events were more prominent in the group taking loperamide. To measure safety of these medications, NNH was calculated and the result was -10. This would be interpreted as followed: Out of 10 patients treated with racecadotril, one less would experience adverse effects. This means that there is a reduced risk of developing adverse effects on racecadotril than if they were treated with loperamide.

Table 2: Loperamide vs. Racecadotril Prado Study[1]

RBI	ABI	NNT	CI
-0.01	-0.01	-100	95% (50-65) for racecadotril 95% (48-66) for loperamide

RRI	ARI	NNH
-0.41	-0.097	-10

In the Vetal study, there were 157 people with acute diarrhea that participated from 34 different primary care clinics.[2] These patients had experienced diarrhea for a mean duration of 39.4 ± 1.7 hours for the racecadotril group and 41.4±2.0 hours for the loperamide group when they started treatment.[2] Before the completion of the study, eight participants withdrew from the study and the rest were able to follow protocol and complete the study .[2] From those that completed the study, 10 did not complete paperwork correctly and therefore only 147 people were included in the measurement of efficacy of these medications.[2] The mean duration of diarrhea for both treatments were very similar with 14.9±2.0 hours for racecadotril and 13.7± 2.2 hours for loperamide.[2] The overall clinical response in this study was similar to each other with 83.7% for patients on racecadotril and 82.2% for patients on loperamide.[2] Results for calculations of efficacy and safety can be seen in Table 3. The NNT for this study for 67 and is interpreted as followed: For every 67 patients treated with racecadotril instead of loperamide,

one additional patient will have complete resolution of symptoms. Adverse events monitored in this study were the same as in the Prado study with most of the cases being rebound constipation. In this study, 7.4% of patients taking racecadotril and 12% of patients taking loperamide experienced adverse events. The NNH was calculated to be -22 which is interpreted as followed: Out of 22 patients treated with racecadotril, one less would experience adverse effects. Therefore it is thought here also that by taking racecadotril, it will lessen the chance of experiencing adverse effects when compared to loperamide.

Table 3: Loperamide vs. Racecadotril Vetal Study[2]

RBI	ABI	NNT	CI
0.018	0.015	67	95% (79.517-87.883) for racecadotril 95% (77.612-86.788) for loperamide

RRI	ARI	NNH
-0.38	-0.046	-22

In the Wang study, there were 62 people with acute diarrhea that participated from 2 primary care clinics and all received at least one dose of treatment.[3] Out of these participants, only 48 patients were considered to follow exact protocol and truly finish the study.[3] When looking at the PP (per protocol) population, the duration of diarrhea were somewhat close at 19 hours in racecadotril group and 13 hours in the loperamide group.[3] The results of efficacy and safety calculations can be found on Table 4. The clinical success rates here were similar to each other with racecadotril at 95.7% and loperamide at 92.0%. The p-value was 0.3704 which signifies that it is not statistically significant because there is about a 37% chance the diarrhea was resolved by chance and not due to the treatments. The NNT was 27 which and can be interpreted as followed: For every 27 patients treated with racecadotril instead of loperamide, one additional patient will have complete resolution of diarrhea. Adverse events monitored in

this study were constipation, bloody stool, skin itching, and abdominal pain upon palpation. The most significant adverse event was constipation and was mostly seen in the loperamide group with 29% compared to the racecadotril group at 12.9%.[3] The NNH was calculated to be -6 which is interpreted as followed: Out of 6 patients treated with racecadotril, one less would experience adverse effects. Therefore it is also agreed here as before that by taking racecadotril, it will lessen the chance of experiencing adverse effects when compared to loperamide.

Table 4: Loperamide vs. Racecadotril Wang Study[3]

RBI	ABI	NNT	p-value
0.04	0.037	27	0.3704

RRI	ARI	NNH
-0.56	-0.161	-6

DISCUSSION

The mechanisms of racecadotril and loperamide are different from each other but ultimately treat acute diarrhea with similarly rapid resolution. Since both mechanisms are different, this may be the cause of the adverse events seen more in loperamide than racecadotril. Loperamide acts as an agonist in the μ-opioid receptor in the gut which causes the transit time to increase allowing the gut to reabsorb more completely and making the stool less watery.[1] When stimulated, these receptors also cause intestinal dilation and decreased peristalsis which could be related to why these patients experience more abdominal distention and constipation.[1] On the other hand, racecadotril inhibits the enzyme enkephalinase.[1] This enzyme inhibits the enkephalins in the GI tract and therefore increases intestinal antihypersecretory action of the δ-receptor agonists.[1] Since racecadotril is affecting different receptors, it does not increase intestinal transit time and therefore causes fewer adverse events as seen in these studies.[1]

Racecadotril is currently not approved to be used in the United States. In May 2007, the WHO submitted a proposal to have racecadotril become part of the WHO essential medicine list

and is still awaiting approval. Even though racecadotril is not approved by the FDA, it has been approved and widely used in European countries since 1993.[6] Recently in October 2012, a brand name of racecadotril was released named Hidrasec in the UK.[8] Currently it costs about 8.42 euros for a pack of 20 tablets which converts to about $10.98 here in the US.[8] Loperamide costs about $9.00 for a pack of 18 tablets. Therefore this shows that both medications are relatively inexpensive and has equal efficacy.

The MHRA and CHM are responsible for regulating this medication in the UK Included in the summary of racecadotril characteristics set forth by these agencies are the following: Racecadotril is currently only known and used to treat acute diarrhea.[8] Since there have not been many studies with this medication, patients with renal or hepatic insufficiency should use this medication with caution.[8] There is no dosage adjustment needed when using this medication in the elderly population.[8] A special warning/precaution on this medication informs patients that it contains lactose.[8] Therefore, patients that are lactose intolerant are warned not to take this medication.[8]

CONCLUSION

Racecadotril has been clinically shown to be as equally effective as loperamide in the treatment of acute diarrhea in these three RCT studies. On the other hand, Loperamide caused more adverse events in these studies when compared to racecadotril. So even though loperamide is as effective as racadotril in resolving acute diarrhea, the patient is more at risk of having adverse events such as constipation, abdominal distention, and nausea/vomiting.

In future studies comparing these medications, larger study groups should be done in order to get more accurate data. Also, all these studies were performed in Taiwan, France, and underdeveloped countries in Latin America. Future studies should include study groups in

different areas of the United States. This could make it possible to develop more data that could show enough evidence to have this medication approved to treat acute diarrhea here in the United States.

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